Lung rejection after transplantation

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With the introduction of Cyclosporine as an immunosuppressive agent, combined heart and lung transplantation (HLTx) became an effective treatment for severe pulmonary vascular disease [1] and has been extended successfully to treat end-stage lung disease [2] and cystic fibrosis [3, 4]. Single lung transplantation offers a treatment for cryptogenic fibrosing alveolitis [5]. It was initially believed that endomyocardial biopsy, a technique used to detect rejection in cardiac transplantation [6], could be used to monitor rejection in HLTx [1]. This proved not to be the case as in both experimental [7] and clinical studies [8] the lungs undergo rejection before the heart. Most centres therefore had to rely on clinical evidence of lung rejection which probably accounted for the high incidence of the principal problem, obliterative bronchiolitis [9] which in some centres has led to disability and death in 50% of long-term survivors [10] of heart-lung transplantation. A similar incidence of obliterative bronchiolitis has now been reported in an early series of single lung transplant patients [11]. A means of repeatedly obtaining lung tissue for histology was required coupled with a non-invasive means of monitoring pulmonary graft function. The lungs paradoxically lend themselves to this, as physiological measurement of their function is highly developed and the methods are easily performed and predictable. Methods for repeated biopsy are also well established.

Transbronchial biopsy (TBB) performed through a fibre-optic bronchoscope is used to diagnose diffuse malignancy of the lung and interstitial lung disease such as sarcoidosis [12] both of which have a distinctive pathological pattern. To overcome sampling error, multiple biopsies, at least four in number [13], are needed. The introduction of larger alligator forceps has enabled bigger samples of tissue to be obtained than with standard cusped forceps.

It has proved possible to apply transbronchial lung biopsy to lung transplantation to distinguish opportunistic pulmonary infection from rejection of the lung [14]. For rejection the technique has a sensitivity of over 70% and a specificity of 100% [15]. In rejection a characteristic histological appearance of perivascular infiltrate consisting mainly of pyrinophilic lymphocytes [16] is seen clearly on TBB, being comparable to the changes observed on open lung biopsy and post mortem studies [17]. Treatment with augmented immunosuppression in the form of intravenous methyl prednisolone 0.5–1.0 g daily for 3 days followed by 1 mg/kg/day oral prednisolone leads to a resolution of these changes [17].

From retrospective analysis it has proved possible to demonstrate at the time of acute lung rejection or pulmonary infection that dynamic lung volumes FEV1, FEV1/FVC, and also TLC fall [18]. By contrast peak expiratory flow, an index of airflow obstruction, fails to change predictably. The former measurements do behave predictably so it is now possible, on a daily basis to closely monitor FEV1, and VC in each patient using a hand held battery operated turbine spirometer [19]. Consistent reductions provide an indication for TBB [18, 20]. The chest radiograph may show no abnormality in up to 60% of rejection episodes [14, 20].

The development of disabling or fatal obliterative bronchiolitis in heart-lung transplants appears to be the result of repeated rejection [21] perhaps promoted by infection particularly of cytomegalovirus (CMV) [22]. Avoidance of primary CMV pneumonitis by not using donors with positive CMV serology [23] may lessen the problem. Early and accurate diagnosis of acute lung rejection with lung function monitoring and TBB, together with effective augmentation of immunosuppression may also reduce the problem. These new approaches have been associated with impressive survival figures and a low incidence (8%) of obliterative bronchiolitis [24]. There remains a small group of patients who develop this disabling condition. Sequential lung biopsy reveals a different pathological appearance from simple acute lung rejection. Early after surgery their biopsies show intra-alveolar lymphocytic and neutrophilic infiltrates. The infiltrates progress to intra-alveolar fibrosis and obliterative bronchiolitis [25]. New immunosuppressive regimes may be required [26].

Heart-lung transplantation has now emerged from its early development phase as another form of organ transplantation. With improved systems of lung preservation [27, 28] organs can be procured from distant hospitals with organ ischaemic times comparable for cardiac transplantation. Excellent early [27, 28] and late graft [2, 3] function have been reported. Non invasive physiological monitoring and repeated TBB render the outlook for this form of transplantation comparable to that of other organs. Advances in immunosuppressive regimes will undoubtedly improve further the effectiveness of heart-lung transplantation.

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References